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Effects of Chemotherapy and Radiation Therapy on Early Laryngeal Cancers

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Abstract. *Background/Aim: Treatments for early laryngeal squamous cell carcinoma (SCC) include radiotherapy (RT), chemoradiotherapy (CRT), and larynx-preserving surgery. In this study, early laryngeal SCC was treated with RT in patients with stage I (T1N0) tumors and with CRT and docetaxel (DOC) in patients with stage II (T2N0) tumors and the treatment results and effectiveness of the chemotherapy were compared. Patients and Methods: A total of 78 patients with early-stage laryngeal SCC were enrolled in this study. The T1N0 patients received radiation for the primary lesions as outpatients at a total dose of 63-70 Gy. By contrast, the T2N0 patients were hospitalized and treated with CRT, receiving a total radiation dose of 66-70 Gy. Docetaxel (DOC, 10 mg/m^2) was administered intravenously once a week for 6-8 consecutive weeks concurrently with radiotherapy. The adverse events and survival rates with local control rates were examined. Results: The number of non-glottic T2N0 patients was significantly higher than that of T1N0 patients. Although all patients completed their treatment schedule, significantly more grade 3 adverse events were observed in the T2N0 patients, in particular mucositis and dermatitis, than in T1N0 patients. The 5-year overall survival rate, disease specific survival rate, local control rate, and laryngeal preserve rate of the T1N0 and T2N0 patients were 86.1, 93.3, 88.6, and 94.3% and 85.9, 88.0, 93.1, and 93.1%, respectively. Conclusion: CRT with docetaxel showed the best therapeutic outcomes for the treatment of laryngeal SCC in patients with T2N0 tumours, with a higher local control rate, effective laryngeal preservation, and relatively few adverse events.*

Laryngeal cancer is among the most common types of head and neck cancer in the world. Its most frequent pathological type is squamous cell carcinoma (SCC), and several risk factors for the pathogenesis of laryngeal cancer have been reported. The most significant risk factors of this disease are tobacco and alcohol consumption (1, 2). Because of the critical role laryngeal function plays in voice production and swallowing, laryngeal cancer has a significant social importance, especially concerning quality of life for afflicted patients (1). Thus, although laryngeal preservation is an important benchmark of laryngeal cancer treatments, advanced-stage laryngeal cancer is typically treated with chemoradiotherapy (CRT) or laryngectomy to achieve better survival rates (1, 2). By contrast, early-stage laryngeal SCC is often treated using radiotherapy (RT), CRT, or larynx-preserving surgery, favoring therapeutic strategies that preserve laryngeal function (1, 2). On the other hand, a previous report showed that patients with early-stage laryngeal cancer treated with surgical therapy had better survival outcomes than patients treated with non-surgical therapy (3).

In our institution, early laryngeal SCC is treated either with RT in patients with T1N0 tumors or with CRT and docetaxel (DOC) in patients with T2N0 tumors. In this study, we retrospectively evaluated the treatment outcomes of our patients and compared the effects of chemotherapy and radiotherapy.

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Key Words: Laryngeal squamous cell carcinoma, early stage, radiation therapy, concurrent chemotherapy, treatment outcomes.

Patients and Methods

Patients. A total of 78 patients with early-stage (T1N0, T2N0) laryngeal cancer were initially treated with radiation therapy between 2011 and 2020 at Iwate Medical University Hospital. Patient information was recorded and stored in a digital medical record system, which was subsequently updated whenever a clinical event occurred. The database was regularly updated. All the patients had histopathologically proven SCC originating from glottis, supra-glottis, or sub-glottis. A summary of the clinical characteristics of each patient is provided in Table I. The ages of the patients were distributed between 51-90 years old, with a median age of 64 years among 72 male and 6 female patients. The cohort comprised 61 patients with glottic cancers, 15 with supra-glottic cancers, and two with sub-glottic cancers. The observation period ranged from 2 to 133 months, with a median of 43.5 months.

Treatment methods. Stage I (T1N0) patients were treated with RT. These patients were administered radiation for their primary lesions as outpatients, with 2.0-2.25 Gy single daily fraction five times a week for a total dose of 63-70 Gy. By contrast, stage II (T2N0) patients were hospitalized and treated with CRT, receiving radiation for their primary lesions with 2.0-2.2 Gy single daily fraction five times a week for a total dose of 66-70 Gy. Docetaxel (DOC, 10 mg/m^2) was administered intravenously once a week for 6-8 consecutive weeks concurrently with radiotherapy. The adverse events were evaluated and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0, 2017).

Study design. This study was designed as a retrospective review of the patients' medical records with the approval of our institutional review board (MH2020-209) and conducted in accordance with the ethical guidelines of the responsible committee on human experimentation (institutional and national), adhering to the principles outlined in the Declaration of Helsinki of 1975, as revised in 2008 (4). Written informed consent was obtained from all patients.

Statistical analysis. Statistical analysis was performed using the chi-squared test for patient distribution. The Kaplan–Meier method was used to calculate the patients' overall survival rate (OS), disease specific survival rate (DSS), local control rate (LCR), and laryngeal preserve rate (LPR). The log-rank test was used to examine significant differences. Differences were considered statistically significant at $p<0.05$.

Results

The clinical characteristic of the stage I (T1N0) and stage II (T2N0) patients with laryngeal SCC in our hospital are summarized in Table I. There were one female and 36 male patients in the T1N0 group and five females and 36 males in the T2N0 group. With regards to the female/male ratio, no significant differences were observed between the groups. There were 34 (91.9%) glottis cancer and three (8.1%) supraglottic cancer patients in the T1N0 group compared to 27 (65.8%) glottis, 12 (29.3%) supraglottic, and two (4.9%) subglottic cancers in the T2N0 group. A comparison between the number of patients with glottic cancer and those with non-glottic cancer revealed a significant difference between the T1N0 and T2N0 groups ($p=0.005$).

Table I. *Characteristics of the patients*.

	Stage I (T1N0) 37	Stage II (T2N0) 41	*p*-Value
Sex			
Male	36	36	0.12
Female	1	5	
Mean age	69.2	68.8	
Subsite			
Supraglottis	3	12	0.005
Glottis	34	27	Glottic *vs.*
Subglottis	0	2	non-glottic

Table II. *Adverse events of the patients*.

	Stage I (n=37)			Stage II (n=41)			
Grade	1	2	3	1	2	3	*p*-Value
Mucositis	15	20	1	3	15	20	<0.0001
Dermatitis	8	24	4	4	19	17	0.002
Creatinine	3	0	0	7	0	0	
AST/ALT	2	0	0	14	0	1	0.7

AST: Aspartate aminotransferase; ALT: alanine aminotransferase.

As planned, all patients completed their treatment schedule. Table II summarizes the adverse events recorded in each of the patients during the treatment period. More grade 3 adverse events were observed in the T2N0 than the T1N0 group, although no grade 4 adverse events were observed in either group. A significant difference was observed between the two groups of patients with regards to the incidence of mucositis ($p<0.0001$) and dermatitis ($p=0.002$).

A representative case of the T2N0 group is illustrated in Figure 1. The tumor, originally located on the right vocal cord (Figure 1A), disappeared after 70 Gy of concurrent chemoradiotherapy with seven consecutive weeks of DOC administration (Figure 1B).

The number of cause-specific deaths for the T1N0 and T2N0 groups were two and three, respectively, the reasons for which were as follows: (i) in the T1N0 group, one patient experienced local recurrence, while another developed cervical metastasis; (ii) in the T2N0 group, one patient experienced local recurrence, another developed cervical metastasis, and one other experienced multiple metastasis, including cervical recurrence. The OS at five years was 86.1% for the T1N0 group and 85.9% for the T2N0 group (Figure 2), while the DSS at five years was 93.3% and

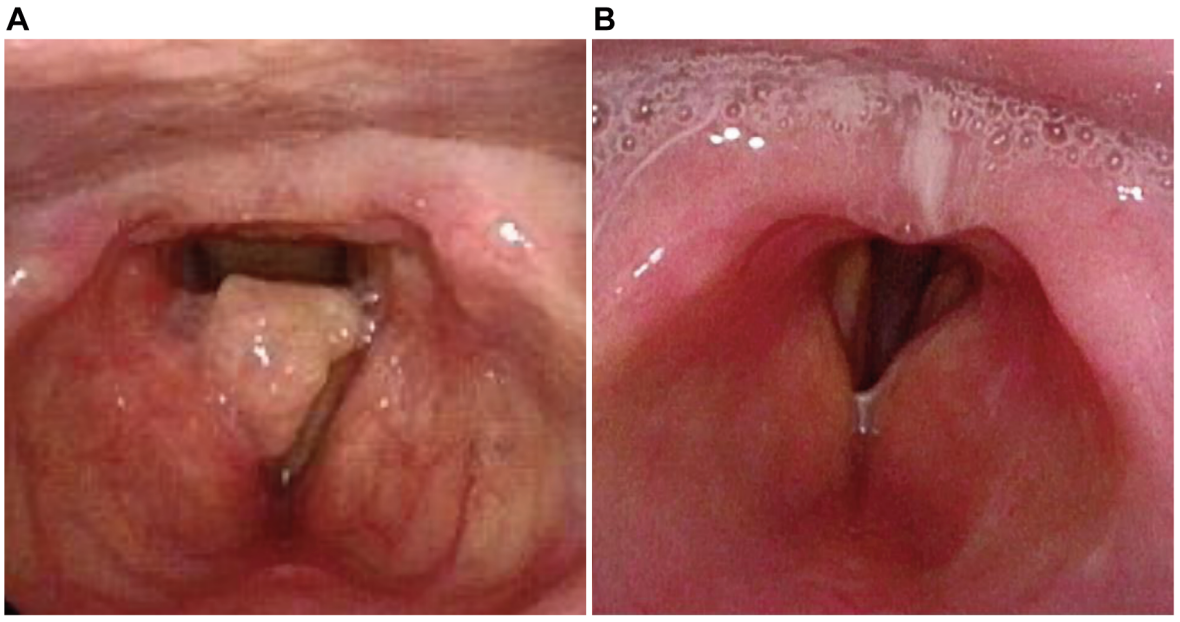

Figure 1. *Representative results of chemoradiotherapy in a T2N0 (Stage II) patient. A) Laryngoscopic image just before treatment and B) after treatment.*

88.0%, respectively (Figure 3). No significant difference was observed between the groups for either metric. By contrast, the LCR at five years was 88.6% for the T1N0 group and 93.1% for the T2N0 group (Figure 4), and although no significant difference was observed between the groups, the T2N0 group showed a higher local control rate. The LPR at five years was 94.3% for the T1N0 group and 93.1% for the T2N0 group (Figure 5), for which no significant difference was observed between the groups.

Discussion

In its early stages, laryngeal cancer is typically treated with a focus on preserving laryngeal function (1, 2, 5) due to the important role larynx plays in many physiological functions, including voice production and swallowing. This is based on evidence that no difference in outcomes exists between patients treated with surgery and those treated with radiotherapy, amongst other common therapeutic treatments for laryngeal SCC (5, 6). Although T1N0 tumors have been previously commonly treated using RT alone, this may be combined with chemotherapy (1, 2) depending on the tumor status and other factors typical of T2N0 tumors. The five-year LCR for T2N0 patients treated with RT alone is 72-78%, worse than that of T1N0 patients (83-92%) (7, 8). However, T2N0 patients treated with CRT have been reported to have a higher five-year LCR of 85-89% (9, 10).

For this study, patients with T2N0 laryngeal SCC in our hospital were treated using CRT after discussion with the pertinent radiologists. A variety of chemotherapy regimens exist for chemoradiotherapy in T2N0 patients (9-15), among which DOC has been reported to achieve best results (9, 12, 15). For example, Furusaka *et al*. reported a five-year OS of 76.8% in a once-weekly DOC group and 96.8% in a twice-weekly DOC group, as well as a five-year LPR of 83.8% in a once-weekly DOC group and 97.6% in a twice-weekly DOC group, as outcomes of CRT for patients with T2N0 glottic SCC (12). In the present study, as the five-year OS and LPR of the T2N0 patients were 85.9% and 93.1%, respectively, our results were compatible with those of previous reports. When compared with patient outcomes after the use of conventional radiotherapy alone in T2N0 patients, our LCR and LPR outcomes were higher than those reported previously (15-17). This may be due to the beneficial effects of DOC administration, as previously reported (12, 15). In addition, there have been several reports that non-glottic laryngeal SCC, such as supraglottic and subglottic laryngeal SCC, show worse oncologic outcomes in patients (2, 5). Although there were significantly more patients with non-glottic cancers in our T2N0 group, the oncological outcomes of the patients with T2N0 tumors were not inferior to those of the patients with T1N0 tumors. These results also suggest that concurrent chemotherapy using DOC had a combinatorial effect on RT for the treatment of T2N0 laryngeal SCC.

In addition, significantly more frequent and severe adverse events were observed in the patients with T2N0 tumors during CRT with DOC than in those with T1N0 tumors. In particular,

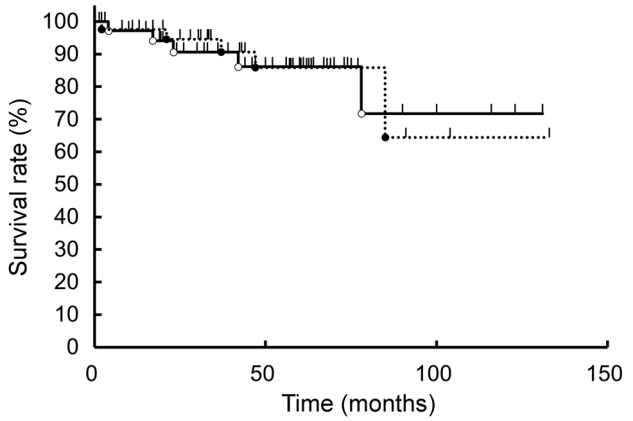

Figure 2. *Kaplan–Meier analysis of the overall survival rates of patients in different clinical stages. The horizontal axis represents the time (months) from treatment and the vertical axis represents the survival rate. Open circle: Stage I. Closed circle: Stage II. The 5-year survival rates of patients with stages I (n=37) and II (n=41) were 86.1 and 85.9%, respectively.*

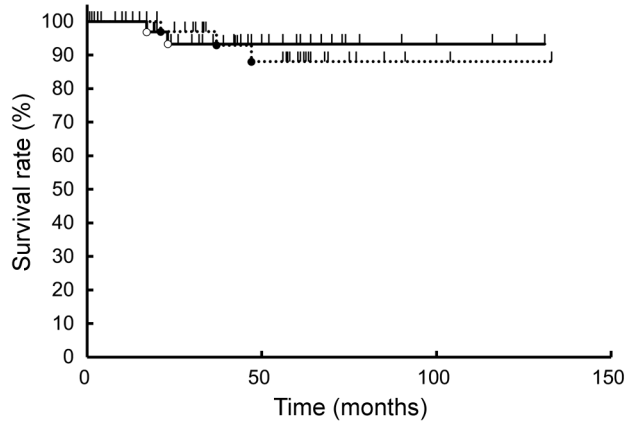

Figure 3. *Kaplan–Meier analysis of the disease-specific survival rates of patients in different clinical stages. The horizontal axis represents the time (months) from treatment and the vertical axis represents the survival rate. Open circle: Stage I. Closed circle: Stage II. The 5-year survival rates of patients with stages I (n=37) and II (n=41) were 93.3 and 88.0%, respectively.*

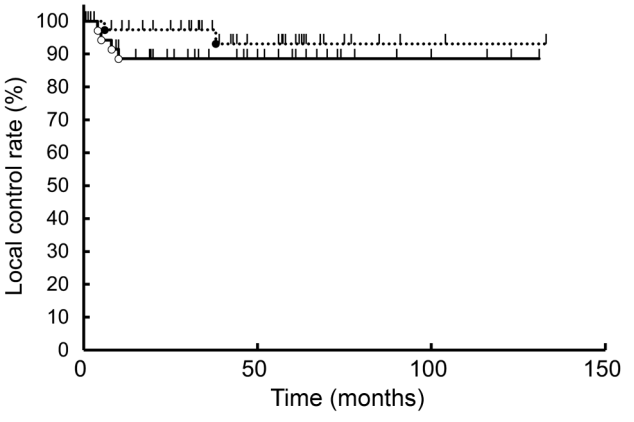

Figure 4. *Kaplan–Meier analysis of the local control rates of patients in different clinical stages. The horizontal axis represents the time (months) from treatment and the vertical axis represents the local control rate. Open circle: Stage I. Closed circle: Stage II. The 5-year local control rates of patients with stages I (n=37) and II (n=41) were 88.6 and 93.1%, respectively.*

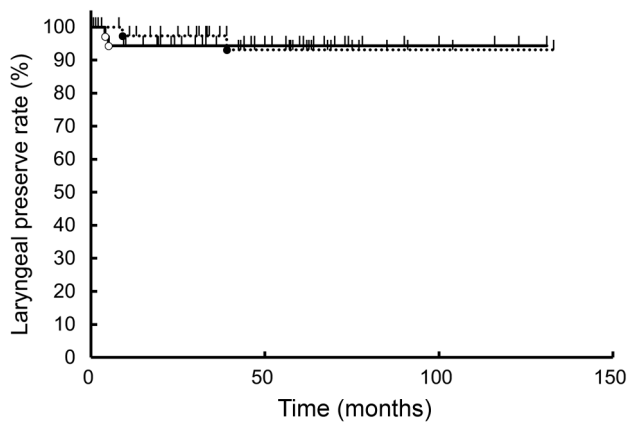

Figure 5. *Kaplan–Meier analysis of the laryngeal preservation rates of patients in different clinical stages. The horizontal axis represents the time (months) from treatment and the vertical axis represents the laryngeal preservation rate. Open circle: Stage I. Closed circle: Stage II. The 5-year laryngeal preservation rates of patients with stages I (n=37) and II (n=41) were 94.3 and 93.1%, respectively.*

the incidences of mucositis and dermatitis were higher and more severe in the former group, a finding that aligns with previous reports (12). However, the frequency and intensity of these adverse events were within acceptable limits of CRT.

Lastly, in the present study, the site of recurrence tended to be the cervical lymph nodes. This may be reflected the fields of RT application in patients with T2N0 tumor. Despite the good LCR of the patients, close follow-up must be conducted after CRT, including imaging follow-up studies of the neck region.

Study limitations. As a retrospective cohort study, relatively few patients were included. Furthermore, a comparison of the efficacy between radiotherapy and chemoradiotherapy in T2N0 patients, resulting in statistical validation, was not performed. However, despite these limitations, substantial results were obtained regarding the concurrent use of chemotherapy in patients with T2N0 laryngeal SCC. The LCR and LPR of our T2N0 patients were better than those in the patients with T1N0 tumors. Although DOC (10 mg/m^2 weekly) was used as concurrent chemotherapy with RT, the

dosage and number of DOC administrations have been varied in the past, and this may need to be reviewed in the future. Further studies using larger patient cohorts and prospective approaches may reveal more specific results for patients with early laryngeal SCC.

Conclusion

Chemoradiotherapy combined with docetaxel treatment in patients with T2N0 laryngeal carcinoma showed a high local control rate, effective laryngeal preservation, and relatively few adverse events.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Conceptualization: K. S.; methodology: K. S. and R. A.; investigation: R. A. and S O; resources: K. T., K. S., K. K., D. S., S. O., A. K.T., I., J. M., T. K., I. K., and H. A.; writing—original draft preparation: R. A. and K. S.; funding acquisition: K. S., K. K., and S. O. All Authors have read and agreed to the published version of the article.

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